Received: 24 October 2023 | Revised: 14 February 2024 | Accepted: 19 February 2024

DOI: 10.1002/jgf2.682

Journal of General and Family Medicine Open Access WILEY

ORIGINAL ARTICLE

SARS-CoV-2 PCR cycle threshold value at admission might not be a good predictor of in-hospital COVID-19-associated AKI

Shiva Rahimipour Anaraki MD[1] | Ali Mohammadian MD[2] | Talieh Mostaghimi MSc[3] | Farzin Sadeghi PhD[4] | Roghayeh Akbari MD[5]

[1]Faculty of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran

[2]Faculty of Medicine, Shahid Beheshti University of Medical sciences, Tehran, Iran

[3]Student Research Committee, Babol University of Medical Sciences, Babol, Iran

[4]Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

[5]Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

Correspondence
Roghayeh Akbari, Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
Email: r.akbari@mubabol.ac.ir

Abstract

Background: Acute kidney injury (AKI) is a prevalent complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and a predictor of disease severity and mortality; furthermore, a prompt diagnosis and treatment of this complication may enhance COVID-19 prognosis. Therefore, we aim to investigate potential risk factors for SARS-CoV-2-associated AKI, including SARS-CoV-2 PCR cycle threshold value (CT value), which correlation with AKI is conflicting.

Methods: This case–control study included 110 hospitalized patients with SARS-CoV-2-associated AKI as cases and 110 random SARS-CoV-2 hospitalized patients as controls. Reverse transcription real-time PCR of admission nasopharyngeal swabs evaluated E gene cycle thresholds. Additional clinical and paraclinical information extracted from medical records. The patient's status at discharge, and 14 and 30 days after discharge. Therefore, after adjusting for age and gender, the correlation between variables was assessed.

Results: SARS-CoV-2 AKI is significantly associated with age above 60, hypertension, diabetes mellitus, ischemic heart disease, and underlying kidney diseases. Abnormal admission hemoglobin or alkaline phosphatase, proteinuria or hematuria in urine sediment, and abnormal creatinine during hospitalization were the paraclinical features correlated to SARS-CoV-2 AKI. AKI group demonstrated greater in-hospital, 14- and 30-day mortality. Nevertheless, this study did not evidence a correlation between the admission CT value and mortality or AKI.

Conclusion: Admission CT values provide limited information regarding the dynamic viral load and varying hospitalization time points; thus, they may not be reliable for predicting the prognosis and complications of COVID-19 in all populations. Further studies with serial CT measurements or symptom onset time adjustment are recommended.

KEYWORDS
acute kidney injury, coronavirus disease 2019, viral load

1 | INTRODUCTION

Since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2019, the coronavirus disease-2019 (COVID-19) pandemic wrought widespread devastation on the global health landscape.[1–3] Until recently, multiple waves of SARS-CoV-2 infections have emerged, predominantly attributed to the development of new variants, among which five have raised notable concerns. These variants have been responsible for approximately 7 million deaths and 770 million confirmed cases to date.[4,5]

While COVID-19 primarily affects the respiratory system, it can also impact the cardiovascular, hematological, gastrointestinal, nervous, and urinary systems, including the kidneys.[6–8] Kidney involvement is common, with clinical manifestations ranging from mild proteinuria in over 40% of patients to acute kidney injury (AKI) necessitating renal replacement therapy.[9]

SARS-CoV-2-associated AKI serves as a biomarker of disease severity and is linked to a higher need for intensive care, ventilation, prolonged hospitalization, and increased medical costs.[10,11] Furthermore, it bears unfavorable prognostic implications for survival among COVID-19 patients and ranks as the leading cause of death after acute respiratory distress syndrome in critically ill SARS-CoV-2 patients.[12] Despite the devastating impacts of this complication, its prevalence is noteworthy, affecting 28% of all COVID-19 patients, 48% of those admitted to the ICU, and over 80% of critically ill patients.[13,14]

Given the substantial prevalence, morbidity, and mortality associated with SARS-CoV-2-associated AKI, early diagnosis of this complication can significantly improve the prognosis of COVID-19 patients. Therefore, identifying patients at risk holds particular clinical significance.[15]

In previous assessments, the recommendation to report quantitative test findings instead of providing positive or negative results was made to refine clinical decisions. This recommendation was based on the association between SARS-CoV-2 viral load, disease severity, mortality, and complications, including SARS-CoV-2-associated AKI.[16–18] However, it should be noted that these claims have been the subject of contradiction.[19–21]

Hence, with the expectation of early detection and treatment of this complication, we intend to conduct a case–control study to investigate the significance of viral load, along with patients' characteristics, clinical and paraclinical aspects, in predicting SARS-CoV-2-associated AKI.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Patients hospitalized in the referral hospital, between "February 2020" and "November 2020" with SARS-CoV-2 diagnosis were eligible for this case–control study. Case patients included all 110 patients diagnosed with an AKI during hospitalization, and 110 hospitalized COVID-19 patients without AKI served as the control group randomly. SARS-CoV-2 diagnosis was based on reverse transcription real-time PCR, and AKI diagnosis was performed in the event of an increase in serum creatinine of 0.3 mg/dL or more within 48 h, an increase in serum creatinine of 1.5 times baseline or more within the previous 7 days, or urine output of less than 0.5 mL/kg/h for 6 h, based on KDIGO 2012.[22]

2.2 | Data collection

Admission day hospital samples of nasopharyngeal swabs were transported to the core research laboratory affiliated with the University of Medical Sciences, where the viral nucleic acid was isolated by RNJia Virus Kit (Roje-Technologies, Yazd, Iran). Consequently, reverse transcription real-time PCR was carried out for the E gene using the LightMix Modular SARS-CoV2 RT-PCR kit (Roche, Germany). Finally, the E gene CT value of SARS-CoV-2 was obtained from StepOnePlus real-time PCR System (Applied Biosystems). SARS-CoV-2 PCR CT values greater than or equal to 30 were considered a low viral load, 25–30 was considered a medium viral load, and less than 25 was considered a high viral load. Demographics, clinical and paraclinical aspects, and treatment protocols of patients were extracted from their hospital records. The collected laboratory measurements were for the admission day except for LDH, D-dimer, CRP, PT, PTT, AST, and ALT; the maximum value was obtained for them. For creatinine, the highest value prior to developing AKI was obtained. The data mentioned above, in addition to the condition of patients at discharge, 14 and 30 days after discharge, were subsequently entered for statistical analysis.

2.3 | Statistical analysis

All collected data were inputted into IBM SPSS Statistics version 26.0. Qualitative data were described as absolute frequencies and percentages, and quantitative data were reported as mean and standard deviation or median and interquartile range according to their distribution. The normality of the variables was determined using histograms and the Kolmogorov–Smirnov test. Quantitative variables were compared using the *t*-test for normally distributed variables and the Mann–Whitney *U* test for skewed data. For comparing the mean of more than two groups, analysis of variances (ANOVA) was used. The distribution of categorial measurements was assessed using Pearson's chi-squared test. The significance level was considered as a p-value <0.05.

2.4 | Ethics approval

The local ethics committee of the University of Medical Sciences approved this study. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of

Helsinki and its later amendments. Written consent was obtained from all included participants.

3 | RESULTS

3.1 | Baseline characteristics in case and control groups

Between February and November 2020, 110 hospitalized patients with SARS-CoV2 laboratory-confirmation developed AKI in Babol, Iran. All of the patients were affected by ancestral Wuhan-like strain of SARS-CoV-2. We compared this group with 110 randomly selected SARS-CoV-2 patients hospitalized in the same hospital and diagnosed based on reverse transcription real-time PCR. Females accounted for 121 (55%) cases, and 116 (52.7%) patients were 60 years or above. There was no significant difference in gender between the AKI (case) and non-AKI (control) groups, although the proportion of patients aged 60 years or older in the AKI group was significantly higher ($p=0.73$, 0.04, respectively) (Table 1).

Diabetes mellitus, hypertension, ischemic heart disease, and underlying kidney disease were the comorbidities with greater odds of developing AKI, whereas a history of malignancy, rheumatologic diseases, chronic obstructive pulmonary disease, and previous kidney transplant was not. Additionally, previous immunosuppressive use did not significantly affect the AKI probability (Table 1).

3.2 | Disease characteristics and prognosis in case and control groups

There was no correlation between the disease's first symptom and AKI's occurrence ($p=0.072$). Patients with cough as a symptom were less prone to develop AKI during admission time ($p=0.026$), whereas other symptoms were not significantly different between the case and control groups. Furthermore, no correlation between initial oxygen saturation and developing AKI was detected ($p=0.29$) (Table 1).

Among laboratory data, the presence of hematuria or proteinuria and an aberrant hemoglobulin, platelet count, alkaline phosphatase at admission, or abnormal creatinine before AKI were all correlated with a higher likelihood of AKI. In addition, an abnormal prothrombin time was observed more in the AKI group. Other laboratory data were not associated with AKI, as shown in Table 2. Notably, chest tomography results did not differ significantly comparing case and control groups ($p=0.66$).

Among 213 patients with accessible information, 211 had received COVID-19 treatment, and only one patient in each group had not. In 181 (85%) patients (84.1% of controls and 85.2% of cases), Kaletra and Chloroquine were administered as the most prevalent treatment protocol. A combination of Azithromycin and Chloroquine was used in 18 (8.4%) patients (7.6% of controls and 9.2% of cases). Other treatment protocols were reported in <5% of patients. In this study, 44 (40.0%) of AKI patients required additional treatments, including intravenous immunoglobulin (IVIg) in 32 patients (29.1%), hemoperfusion in 8 patients (7.3%), and methylprednisolone and hyperimmune plasma each in two patients (1.8%). In comparison, 13 (12%) of non-AKI patients received these treatments, comprising IVIg in 11 patients (10%) and methylprednisolone in 2 patients (1.8%), with neither hyperimmune plasma nor hemoperfusion necessitated. The AKI group required the mentioned treatments significantly more, with a p-value of <0.001.

Cases were more likely than controls to be hospitalized for more than 10 days or undergo mechanical ventilation ($p=0.003$, 0.049, respectively). AKI group had higher mortality and lower complete recovery, in-hospital, 14-day, and 30-day mortality rates, and during hospitalization, 14 or 30 days after discharge ($p=0.005$, 0.020, and 0.004, respectively).

3.3 | Admission's day SARS-CoV-2 PCR cycle threshold value by patients' characteristics and prognosis

Table 3 demonstrates SARS-CoV-2 PCR CT values by participants' characteristics. Greater CT values were observed in patients older than 60 years; however, there was no correlation between gender and CT values. Additionally, comorbidities, including underlying kidney disease, diabetes mellitus, hypertension, ischemic heart disease, malignancies, chronic obstructive pulmonary disease, and rheumatologic diseases, were not associated with the CT value on admission day.

Comparing CT values following the first symptom, cough as an initial symptom was related to greater CT values than fever ($p=0.014$, mean difference = 4.22). Among the symptoms, the absence of myalgia was correlated with higher CT values ($p=0.006$, mean difference = −2.01). The admission oxygen saturation was not associated with the CT value simultaneously. Patients' para clinics, including blood tests, urine analysis, and chest CT, were not associated with CT values, except for D-dimer. The mean CT value was 19.95 for patients with an abnormal peak of D-dimer and 33.71 for patients with a normal D-dimer ($p=0.002$).

This study did not demonstrate a correlation between mortality, hospitalization duration, or mechanical ventilation with admission CT values, neither quantitatively nor qualitatively, after adjusting for age and gender. Furthermore, admission CT values were not associated with COVID-19 treatment protocols administered during hospitalization ($p=0.073$).

3.4 | Admission's day SARS-CoV-2 PCR cycle threshold value by developing AKI

Eighty percent of case patients had low CT values, 14.3% had medium values, and 5.7% had high values, compared to 73.9%, 18.5%,

TABLE 1 Characteristics of the AKI cases and controls.

	Cases (AKI)	Controls (non-AKI)	*p*-Value	Number of cases/controls with measurement
Male, *n* (%)	59 (53.6%)	62 (56.3%)	0.7	110/110
Age >60 years, *n* (%)	66 (60%)	50 (45.4%)	0.04	110/110
Clinical comorbidities, *n* (%)				
Chronic obstructive pulmonary disease	9 (8.1%)	5 (4.5%)	0.2	110/110
Diabetes mellitus	53 (48.1%)	30 (27.2%)	0.001	
Hypertension	66 (60.0%)	21 (19.0%)	<0.001	
Rheumatologic diseases	3 (2.7%)	2 (1.8%)	0.7	
Malignancy	5 (4.5%)	2 (1.8%)	0.3	
Underlying kidney disease	48 (43.6%)	9 (8.1%)	<0.001	
Kidney transplant	10 (9.0%)	6 (5.4%)	0.2	
Use of immunosuppressive medications, *n* (%)	9 (8.1%)	6 (5.4%)	0.3	110/110
First Symptom, *n* (%)				
Cough	6 (20.0%)	19 (38.0%)	0.07	30/50
Fever	8 (26.6%)	5 (10.0%)		
Dyspnea	14 (46.6%)	26 (52.0%)		
Diarrhea	1 (3.3%)	0		
Body pain	1 (3.3%)	0		
Symptoms, *n* (%)				
Cough	73 (66.3%)	88 (80%)	0.026	110/110
Dyspnea	85 (77.2%)	93 (84.5%)	0.1	
Sore throat	16 (14.5%)	18 (16.3%)	0.7	
Fever	76 (69.0%)	84 (76.3%)	0.1	
Chills	57 (51.8%)	62 (56.3%)	0.5	
Nausea/Vomiting	20 (18.1%)	21 (19.0%)	0.8	
Diarrhea	4 (3.6%)	7 (6.3%)	0.4	
Body pain	32 (29.0%)	40 (36.3%)	0.2	
Anosmia	1 (0.09%)	1 (0.09%)	–	
First oxygen saturation <93%, *n* (%)	74 (69.8%)	65 (63.1%)	0.2	106/103
Mechanical ventilation, *n* (%)	30 (27.2%)	18 (16.3%)	0.049	
Duration of hospitalization >10 days, *n* (%)	30 (27.2%)	11 (10.0%)	0.003	110/110
In-hospital mortality, *n* (%)	40 (36.3%)	21 (19.0%)	0.005	110/110
Condition 14 days after discharge, *n* (%)				
Asymptomatic	66 (60.0%)	85 (77.2%)	0.020	110/110
Symptomatic	4 (3.6%)	4 (3.6%)		
Death	40 (36.3%)	21 (19.0%)		
Condition 30 days after discharge, *n* (%)				
Asymptomatic	67 (60.9%)	89 (80.9%)	0.004	110/110
Symptomatic	2 (1.8%)	0		
Death	41 (37.2%)	21 (19.0%)		

and 7.6% for control patients. The correlation between qualitative PCR and AKI was insignificant ($p = 0.597$). Furthermore, the quantitative value of the admission day's CT value was not significantly associated with an AKI during hospitalization ($p = 0.227$). After adjusting for age and gender, the results remained statistically insignificant.

4 | DISCUSSION

This case–control study was designed to examine the significance of admission SARS-CoV-2 PCR CT value in addition to patients' characteristics, clinical and paraclinical aspects in predicting SARS-CoV-2-associated AKI and demonstrated that

TABLE 2 Paraclinical aspects of the AKI cases and controls.

Variable			Cases (AKI)	Controls (non-AKI)	*p*-Value	Number of cases/controls with measurement
Chest Computed Tomography		Typical for COVID-19	86 (78.1%)	89 (80.9%)	0.66	110/110
		Atypical for COVID-19	21 (19.9%)	17 (15.4%)		
		Normal	3 (2.7%)	4 (3.6%)		
Blood tests	Lymphocytes	Abnormal	38 (36.5%)	36 (33.9%)	0.7	104/106
		Normal	66 (63.4%)	70 (66.0%)		
	Hemoglobin	Abnormal	85 (77.9%)	45 (41.2%)	<0.001	109/109
		Normal	24 (18.3%)	64 (58.7%)		
	Platelets	Abnormal	38 (34.8%)	24 (22.0%)	0.044	109/109
		Normal	71 (65.1%)	85 (77.9%)		
	Creatinine	Abnormal	90 (84.1%)	9 (8.1%)	<0.001	107/110
		Normal	17 (15.8%)	101 (91.8%)		
	Potassium	Abnormal	14 (12.7%)	16 (14.5%)	0.63	110/110
		Normal	96 (87.2%)	94 (85.4%)		
	Phosphorus	Abnormal	3 (2.7%)	2 (1.8%)	0.73	110/110
		Normal	107 (97.2%)	108 (98.1%)		
	Magnesium	Abnormal	20 (18.1%)	18 (16.3%)	0.82	110/110
		Normal	90 (81.8%)	92 (83.6%)		
	AST	Abnormal	43 (45.2%)	45 (46.3%)	0.91	95/97
		Normal	52 (54.7%)	52 (53.6%)		
	ALT	Abnormal	32 (32.3%)	31 (31.3%)	0.85	99/99
		Normal	67 (67.6%)	68 (68.6%)		
	Alkaline phosphatase	Abnormal	73 (80.2%)	53 (56.3%)	0.001	91/94
		Normal	18 (19.7%)	41 (43.6%)		
	LDH	Abnormal	50 (64.1%)	46 (57.5%)	0.4	78/80
		Normal	28 (35.8%)	34 (42.5%)		
	CRP	Abnormal	82 (78.8%)	78 (79.5%)	0.87	104/98
		Normal	22 (21.1%)	20 (20.4%)		
	D-dimer	Abnormal	7 (87.5%)	4 (80.0%)	0.71	8/5
		Normal	1 (12.5%)	1 (20.0%)		
	Procalcitonin	Abnormal	20 (58.8%)	10 (41.6%)	0.19	34/24
		Normal	14 (41.1%)	14 (58.3%)		
	PT	Abnormal	51 (54.2%)	33 (38.3%)	0.039	94/86
		Normal	43 (45.7%)	53 (61.6%)		
	INR	Abnormal	54 (55.6%)	43 (49.4%)	0.4	97/87
		Normal	43 (44.3%)	44 (50.5%)		
	PTT	Abnormal	39 (42.8%)	41 (48.8%)	0.45	91/84
		Normal	52 (57.1%)	43 (51.1%)		
Urine Analysis	Hematuria	Negative	13 (54.1%)	32 (96.9%)	<0.001	24/33
		Positive	11 (45.8%)	1 (3.0%)		
	Proteinuria	Negative	12 (50.0%)	27 (84.3%)	0.013	24/32
		Positive	12 (50.0%)	5 (15.6%)		

Note: The collected laboratory measurements were for the admission day except for LDH, D-dimer, CRP, PT, PTT, AST, and ALT; the maximum value was obtained for them. For creatinine, the highest value prior to developing AKI was obtained.

TABLE 3 Patients' characteristics by E gene cycle thresholds.

Variable			E gene cyclic threshold	*p*-Value
Gender		Male	31.52 ± 4.24	0.45
		Female	31.03 ± 5.24	
Age group (years)		≤60	30.50 ± 5.17	0.022
		>60	31.99 ± 4.18	
Comorbidity	COPD	No	31.38 ± 4.78	0.32
		Yes	30.05 ± 3.47	
	DM	No	31.10 ± 4.99	0.76
		Yes	31.61 ± 4.26	
	HTN	No	31.01 ± 4.78	0.29
		Yes	31.71 ± 4.62	
	IHD	No	30.77 ± 4.44	0.30
		Yes	31.51 ± 4.82	
	Rheumatologic diseases	No	31.30 ± 4.77	0.91
		Yes	31.08 ± 1.38	
	Malignancy	No	31.25 ± 4.7	0.46
		Yes	32.58 ± 5.31	
	Underlying Kidney disease	No	31.27 ± 4.36	0.89
		Yes	31.37 ± 5.62	
	Kidney transplant	No	31.43 ± 4.64	0.15
		Yes	29.62 ± 5.55	
History of immunosuppressive consumption		No	31.40 ± 4.65	0.25
		Yes	29.92 ± 5.63	
First symptom		Cough	33.96 ± 3.92	0.019
		Fever	28.83 ± 4.90	
		Dyspnea	31.52 ± 4.28	
Symptoms	Cough	Negative	31.45 ± 4.89	0.77
		Positive	31.24 ± 4.66	
	Dyspnea	Negative	31.50 ± 4.72	0.76
		Positive	31.25 ± 4.73	
	Sore throat	Negative	31.51 ± 4.56	0.13
		Positive	30.14 ± 5.44	
	Fever	Negative	31.74 ± 4.89	0.20
		Positive	31.13 ± 4.66	
	Chills	Negative	31.52 ± 4.83	0.52
		Positive	31.10 ± 4.63	
	Nausea/Vomiting	Negative	31.36 ± 4.70	0.68
		Positive	31.02 ± 4.84	
	Diarrhea	Negative	31.33 ± 4.78	0.61
		Positive	30.56 ± 3.30	
	Body pain	Negative	31.95 ± 4.37	0.006
		Positive	29.93 ± 5.14	
	Anosmia	Negative	31.26 ± 4.72	0.26
		Positive	35.05 ± 2.75	
First oxygen saturation		<93	31.33 ± 4.85	0.96
		>=93	31.37 ± 4.59	
Mechanical ventilation		No	31.08 ± 4.93	0.15
		Yes	32.05 ± 3.81	
Duration of hospitalization (days)		=<10	31.19 ± 4.73	0.30
		>10	32.09 ± 4.78	
Discharge condition		Alive	31.12 ± 5.02	0.32
		Death	31.76 ± 3.84	
Condition 14 days after discharge		Asymptomatic	31.03 ± 5.08	0.50
		Symptomatic	32.70 ± 3.47	
		Death	31.76 ± 3.84	
Condition 30 days after discharge		Asymptomatic	31.09 ± 5.06	0.86
		Symptomatic	32.55 ± 0.77	
		Death	31.76 ± 3.81	
Acute kidney injury		case	31.67 ± 4.60	0.20
		control	30.88 ± 4.83	
Chest Computed Tomography		Typical for COVID-19	31.30 ± 4.87	0.27
		Atypical for COVID-19	31.80 ± 3.86	
		Normal	28.67 ± 4.72	

SARS-CoV-2-associated AKI is significantly associated with age >60, specific comorbidities, and laboratory abnormalities. Furthermore, AKI patients, compared with non-AKI patients, required more additional interventions and had higher mortality rates. Nevertheless, this study did not evidence a correlation between admission SARS-CoV-2 PCR CT value and mortality or the AKI. These findings warrant further discussion.

SARS-CoV-2-associated AKI was correlated with poor prognosis and an increased mortality rate.[12,23] Likewise, the AKI group in this study had significantly more extended hospital stays and higher in-hospital, 14-day, and 30-day mortality rates. Understanding risk factors can assist physicians in identifying at-risk patients and, due to early detection, enhance the prognosis. Consequently, the present study assessed risk factors for AKI and highlighted several significant ones. Some risk factors, including aging, DM, HTN, IHD, and underlying kidney disease, are well established.[24,25] Even though abnormal creatinine, abnormal admission hemoglobin, proteinuria, and hematuria are less known.[26–28] Remarkably, this study established an abnormal alkaline phosphatase (ALP) at admission as a predictor of SARS-CoV-2-associated AKI. ALP is negatively associated with glomerular filtration rate and positively associated with proteinuria in diabetic patients. Some studies are presently evaluating the effect of ALP on the incidence of AKI in sepsis or surgical patients.[29] Subsequently, we propose the correlation between ALP and SARS-CoV-2-associated AKI as an additional intriguing area of research.

Previously, many studies suggested a correlation between SARS-CoV-2 viral load and the severity of the disease; however, others

failed to validate a correlation. A recent systematic review discovered that several studies supported or opposed this association.[19] Similarly, there is controversy among the articles that evaluated the correlation between viral load and SARS-CoV-2-associated AKI.[17,20] Paranjpe et al., in a retrospective cohort study, reported that the admission day's viral load was weakly but significantly associated with AKI. In contrast, Rajyalakshmi et al., in a retrospective study, concluded that the admission's CT value was not correlated with AKI.[17,20] This study found no association between the admission CT value and AKI. This discrepancy can be attributed to several factors.

First, SARS-CoV-2 viral load alters throughout the illness due to dynamic interaction with the host's immune response, leading to a significant correlation between viral load and the sampling time relative to the onset of symptoms.[30] Viral load in the upper respiratory system spikes before or in the early days of symptom onset.[30] Moreover, hospitalization protocols differ from country to country based on the healthcare system's capabilities; consequently, patients were admitted to the hospital at varying times from onset. Consequently, CT values may or may not be representative of peak CT values in different studies. Hence, various admitting times may contribute to this disparity. Further studies with sampling time adjustment according to symptoms onset or serial CT measurements will provide more detailed information.

Second, there are multiple etiologies related to SARS-CoV-2-associated AKI. Some are caused by virus-specified responses, including direct infection with virus renal tropism, local and systemic inflammation, endothelial injury, and renin-angiotensin system, while others are general responses to critical disease or its treatment.[24,31] The viral load may play a crucial role in specific etiologies; however, in others, it may not. Consequently, this disparity may be attributed to the varying proportion of AKI underlying causes across populations.

Third, racial and ethnic disparities in COVID-19 prognosis have been documented.[32,33] Furthermore, ACE2 polymorphisms and APOL1 genotype are genetic risk factors for SARS-CoV-2-associated AKI.[24] Thus, genetic and ethnic factors may additionally contribute to these variances.

Additionally, this study documented that patients who experienced myalgia as a symptom had significantly lower CT values. In a case-sectional study, Tharwat et al. concluded that musculoskeletal symptoms are associated with COVID-19 severity.[34] Adam Kucuk hypothesized antiviral therapies and viral load reduction to treat myalgia in COVID-19 patients when painkillers were ineffective.[35] The information mentioned above highlights the importance of assessing the pathophysiology and prognosis of myalgia in COVID-19 patients.

This study was a case–control study in which all the patients who developed SARS-CoV-2-associated AKI in an Iranian city were included; however, it had certain limitations. This study included a single-time CT value measurement, and as patients presented to the hospital at varying stages of the disease, CT measurements may not indicate the peak values. Additional studies with serial measurements or a time adjustment based on the symptom onset are suggested. Although adjusting for age and gender, patients' comorbidities, drug histories, and medications prior to hospitalization may bias the results. Furthermore, it is worth noting that the total numbers of each blood test varied, and there was a significantly restricted number of patients who were receiving certain blood laboratory tests, such as D-dimer and procalcitonin, and the results for them may not be conclusive. Additionally, these results may not apply to all ethnicities and all SARS-CoV-2 variants; further studies on other ethnic populations and other viral variants are recommended.

5 | CONCLUSION

This study did not evidence a significant correlation between the admission SARS-CoV-2 PCR CT value and SARS-CoV-2-associated AKI or mortality rate. Hence, admission viral load may not be reliable for predicting the prognosis and complications of COVID-19 in all populations, given the discrepancies among conducted studies and the fact that a single-point quantitative test at admission provides limited information regarding the dynamic viral load and various hospitalization time points.

FUNDING INFORMATION

No funding was received for this study.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

The local ethics committee of Babol University of Medical Sciences approved this study (IR.MUBABOL.REC.1399.515). The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

PATIENT CONSENT STATEMENT

Written consent was obtained from all included participants.

CLINICAL TRIAL REGISTRATION

None.

ORCID

Shiva Rahimipour Anaraki https://orcid.org/0000-0001-6353-7727
Ali Mohammadian https://orcid.org/0000-0001-7586-4282
Farzin Sadeghi https://orcid.org/0000-0001-8599-3643
Roghayeh Akbari https://orcid.org/0000-0002-3720-3077

REFERENCES

1. ILO, IFAD, WHO. Impact of COVID-19 on people's livelihoods, their health and our food systems. 2020 Accessed October 13, 2020. Available from: https://www.who.int/news/

item/13-10-2020-impact-of-covid-19-on-people's-livelihoods-their-health-and-our-food-systems
2. Bidari A, Asgarian S, Pour Mohammad A, Naderi D, Anaraki SR, Gholizadeh Mesgarha M, et al. Immune thrombocytopenic purpura secondary to COVID-19 vaccination: a systematic review. Eur J Haematol. 2023;110(4):335–53.
3. Kurihara M, Kamata K, Nakahara S, Kitazawa K, Koizumi S, Tokuda Y. Healthcare use and RT-PCR testing during the first wave of the COVID-19 pandemic in Japan. J Gen Fam Med. 2022;23(1):3–8.
4. Mohseni Afshar Z, Tavakoli Pirzaman A, Karim B, Rahimipour Anaraki S, Hosseinzadeh R, Sanjari Pireivatlou E, et al. SARS-CoV-2 Omicron (B.1.1.529) Variant: A Challenge with COVID-19. Diagnostics (Basel). 2023;13(3):559. https://doi.org/10.3390/diagnostics13030559
5. WHO. WHO coronavirus (COVID-19) dashboard. These variants have been responsible for approximately 7 million deaths and 770 million confirmed cases to date. 2023. Accessed March 3, 2024. Available from: https://covid19.who.int/
6. Nogueira SÁ, Oliveira SCS, Carvalho AFM, Neves JMC, Silva LSVD, Silva Junior GBD, et al. Renal changes and acute kidney injury in covid-19: a systematic review. Rev Assoc Med Bras (1992). 2020;66(Suppl 2):112–7.
7. Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, et al. Organ-specific manifestations of COVID-19 infection. Clin Exp Med. 2020;20(4):493–506.
8. Radkhah H, Mansouri ES, Rahimipour Anaraki S, Gholizadeh Mesgarha M, Sheikhy A, Khadembashiri MM, et al. Predictive value of hematological indices on incidence and severity of pulmonary embolism in COVID-19 patients. Immun Inflamm Dis. 2023;11(9):e1012.
9. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8(7):738–42.
10. Hamilton P, Hanumapura P, Castelino L, Henney R, Parker K, Kumar M, et al. Characteristics and outcomes of hospitalised patients with acute kidney injury and COVID-19. PLoS One. 2020;15(11):e0241544.
11. Cui X, Yu X, Wu X, Huang L, Tian Y, Huang X, et al. Acute kidney injury in patients with the coronavirus disease 2019: a multicenter study. Kidney Blood Press Res. 2020;45(4):612–22.
12. Moledina DG, Simonov M, Yamamoto Y, Alausa J, Arora T, Biswas A, et al. The association of COVID-19 with acute kidney injury independent of severity of illness: a multicenter cohort study. Am J Kidney Dis. 2021;77(4):490–499.e1.
13. Silver SA, Beaubien-Souligny W, Shah PS, Harel S, Blum D, Kishibe T, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis. Kidney Med. 2021;3(1):83–98.e1.
14. Schaubroeck H, Vandenberghe W, Boer W, Boonen E, Dewulf B, Bourgeois C, et al. Acute kidney injury in critical COVID-19: a multicenter cohort analysis in seven large hospitals in Belgium. Crit Care. 2022;26(1):225.
15. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med. 2020;46(7):1339–48.
16. Rao SN, Manissero D, Steele VR, Pareja J. A systematic review of the clinical utility of cycle threshold values in the context of COVID-19. Infect Dis Ther. 2020;9(3):573–86.
17. Paranjpe I, Chaudhary K, Johnson KW, Jaladanki SK, Zhao S, de Freitas JK, et al. Association of SARS-CoV-2 viral load at admission with in-hospital acute kidney injury: a retrospective cohort study. PLoS One. 2021;16(2):e0247366.
18. Kim C, Kim JY, Lee EJ, Kang YM, Song KH, Kim ES, et al. Clinical findings, viral load, and outcomes of COVID-19: comparison of patients with negative and positive initial chest computed tomography. PLoS One. 2022;17(3):e0264711.
19. Dadras O, Afsahi AM, Pashaei Z, Mojdeganlou H, Karimi A, Habibi P, et al. The relationship between COVID-19 viral load and disease severity: a systematic review. Immun Inflamm Dis. 2022;10(3):e580.
20. Rajyalakshmi B, Samavedam S, Reddy PR, Aluru N. Prognostic value of "cycle threshold" in confirmed COVID-19 patients. Indian J Crit Care Med. 2021;25(3):322–6.
21. Ontiveros N, del Bosque-Aguirre A, Gonzalez-Urquijo M, Hinojosa Gonzalez DE, Martinez-Resendez MF, Schang L, et al. Nasopharyngeal viral load at admission is not an independent predictor of thromboembolic complications in unvaccinated COVID-19 hospitalized patients. J Thromb Thrombolysis. 2023;55(2):282–8.
22. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179–c184.
23. Hansrivijit P, Qian C, Boonpheng B, Thongprayoon C, Vallabhajosyula S, Cheungpasitporn W, et al. Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis. J Investig Med. 2020;68(7):1261–70.
24. Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th acute disease quality initiative (ADQI) workgroup. Nat Rev Nephrol. 2020;16(12):747–64.
25. Zhang J, Pang Q, Zhou T, Meng J, Dong X, Wang Z, et al. Risk factors for acute kidney injury in COVID-19 patients: an updated systematic review and meta-analysis. Ren Fail. 2023;45(1):2170809.
26. Marques F, Gameiro J, Oliveira J, Fonseca JA, Duarte I, Bernardo J, et al. Acute kidney disease and mortality in acute kidney injury patients with COVID-19. J Clin Med. 2021;10(19):4599.
27. McAdams MC, Li M, Xu P, Gregg LP, Patel J, Willett DL, et al. Using dipstick urinalysis to predict development of acute kidney injury in patients with COVID-19. BMC Nephrol. 2022;23(1):50.
28. Xu Z, Zhang Y, Zhang C, Xiong F, Zhang J, Xiong J. Clinical features and outcomes of COVID-19 patients with acute kidney injury and acute kidney injury on chronic kidney disease. Aging Dis. 2022;13(3):884–98.
29. Haarhaus M, Cianciolo G, Barbuto S, La Manna G, Gasperoni L, Tripepi G, et al. Alkaline phosphatase: an old friend as treatment target for cardiovascular and mineral bone disorders in chronic kidney disease. Nutrients. 2022;14(10):2124.
30. Challenger JD, Foo CY, Wu Y, Yan AWC, Marjaneh MM, Liew F, et al. Modelling upper respiratory viral load dynamics of SARS-CoV-2. BMC Med. 2022;20(1):25.
31. Legrand M, Bell S, Forni L, Joannidis M, Koyner JL, Liu K, et al. Pathophysiology of COVID-19-associated acute kidney injury. Nat Rev Nephrol. 2021;17(11):751–64.
32. Labgold K, Hamid S, Shah S, Gandhi NR, Chamberlain A, Khan F, et al. Estimating the unknown: greater racial and ethnic disparities in COVID-19 burden after accounting for missing race and ethnicity data. Epidemiology. 2021;32(2):157–61.
33. Mackey K, Ayers CK, Kondo KK, Saha S, Advani SM, Young S, et al. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. Ann Intern Med. 2021;174(3):362–73.
34. Tharwat S, Shabana NM, Nassar MK. Lifting the mask on musculoskeletal manifestations of COVID-19: results of an interview-based study. Open Access Rheumatol. 2022;14:211–20.
35. Kucuk A, Cumhur Cure M, Cure E. Can COVID-19 cause myalgia with a completely different mechanism? A hypothesis. Clin Rheumatol. 2020;39(7):2103–4.

How to cite this article: Rahimipour Anaraki S, Mohammadian A, Mostaghimi T, Sadeghi F, Akbari R. SARS-CoV-2 PCR cycle threshold value at admission might not be a good predictor of in-hospital COVID-19-associated AKI. J Gen Fam Med. 2024;25:179–186. https://doi.org/10.1002/jgf2.682